PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Wells et al.

Serial No.: 09/691,237

Filed: October 19, 2000

For: SUSTAINED-RELEASE FORMULATIONS FOR TREATING CNS-MEDIATED DISORDERS

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Examiner: L. S. Channavajjala

Group Art Unit: 1615

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APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sirs:

This brief is submitted in the format required by 37 C.F.R. § 41.37(c).

REAL PARTY IN INTEREST

The real party in interest in the present pending appeal is NPS Pharmaceuticals, Inc., assignee of the pending application as recorded with the United States Patent and Trademark Office on January 3, 2001, at Reel 011389, Frame 0166.

RELATED APPEALS AND INTERFERENCES

Neither the Appellants, the Appellants' representative, nor the Assignee is aware of any pending appeal or interference which would directly affect, be directly affected by, or have any bearing on the Board's decision in the present pending appeal.

STATUS OF THE CLAIMS

Claims 1-34, 36, 43, 56, 58 and 59 are cancelled.

Claims 35, 37-42, 44-55 and 57 stand rejected.

No claims are allowed.

The rejections of claims 35, 37-42, 44-55 and 57 are being appealed.

STATUS OF AMENDMENTS

An amendment under 37 C.F.R. § 1.116 was filed on September 30, 2005. An Advisory Action mailed November 4, 2005, notified Appellants that the proposed amendments were not entered because they allegedly raise new issues and purportedly fail to overcome the Examiner's rejections. (*See*, Advisory Action, pp. 1-2).

More particularly, Appellants proposed amending claims 35, 37-42, 44-55 and 57 to clarify the claim language and to remove issues with antecedent basis and formalities. However, the proposed claim amendments were not entered. Specifically, the Examiner stated that the amendment changing the upper limit of one of the ingredients from "about 40-70%" to "about 40% to about 70%" requires further consideration. *Id.* at p.2. As such, Appellants assume that the claims stand as listed previous to the proposed amendments filed on September 30, 2005.

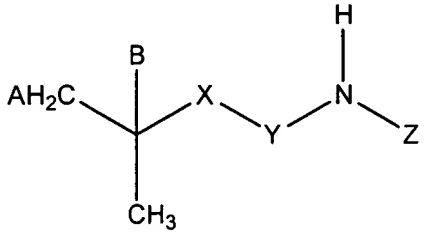
Furthermore, the amendment of September 30, 2005, was filed along with a Rule 132 Declaration to address the obviousness rejection maintained in the Final Office Action mailed April 1, 2005. In that amendment, Appellants asserted that the submission of the Rule 132 Declaration was proper and did not raise new issues because the discussion of the obviousness rejections with the Examiner during an interview on November 30, 2004, led Appellants to believe that the amendment filed December 9, 2004, would overcome the obviousness rejections, thus, making a Rule 132 Declaration unnecessary. (*See*, December 9, 2004, Office Action

Response, pp. 9-10). After considering the Rule 132 Declaration, the Examiner maintained the obviousness rejections, asserting that the Declaration does not present any unexpected results. (Advisory Action, p. 2).

SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed invention relates to the effective treatment of pathological conditions, such as epilepsy, bipolar affective disorder, migraine, anxiety and spasticity, the symptoms of which are alleviated by a modulation of activity in the central nervous system (CNS). The claimed invention provides for the preparation and use of sustained-release formulations of isovaleramide, isovaleric acid, and related compounds for treatment of patients suffering from such pathologies characterized by the abnormal function of the CNS.

More particularly, independent claim 35 recites, in part, an oral sustained-release pharmaceutical composition (*see*, Specification, p. 2, lines 12-30) comprising a core matrix (*Id.* at p. 12, line 25 to p. 13, line 4) comprising a therapeutically effective amount of an active compound (*Id.* at p. 23, lines 2-28) and a gelling agent (*Id.* at p. 13, lines 5-30), wherein the amount of the active compound represents about 40% to 70% by weight of the oral sustained-release pharmaceutical composition (*Id.* at p. 11, lines 10-13), and wherein the active compound is selected from the group consisting of isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isolaveric acid (*Id.* at p. 6, line 14-28), a compound having the structure:



wherein A = H, CH_3, or OH, B = H, OH, or CH_3, X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH), or -CH_2O-, Y = -CO-, or $-SO_2$-, and Z = H, CH_2CO_2H, or CH_2CONH_2, and a compound selected from the group consisting of isovaleramide, 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide,

2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide (*Id.* at p. 7, lines 1-17; *see*, FIGs. 1a. and 1b.), 2-methyl-1-propylsulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate (*see*, Specification p. 8, lines 3-10).

Independent claim 48 recites, in part, a process for preparing an oral sustained-release pharmaceutical composition comprising a core matrix comprising a therapeutically effective amount of an active compound, a gelling agent and optionally one or more substances that further retard the release of the active compound (*Id.* at p. 14, line 1 to page 19, line 15). The process of claim 48 comprises mixing the therapeutically effective amount of an active compound with a gelling agent and optionally one or more substances that further retards the release of the active compound (*Id.* at p. 33, line 20 to p. 34, line13) then compressing or extruding this mixture (*Id.* at p. 34, lines 14-16).

Independent claim 51 recites, in part, a method of treating a pathology that is ameliorated by a modulation of a CNS activity, wherein said pathology is selected from the group consisting of convulsions, spasticity, affective mood disorder, neuropathic pain syndrome, headache, restlessness syndrome, movement disorder, substance abuse/craving, and cerebral trauma (*Id.* at p. 24, line 10 to p. 31, line 19), comprising administering to a patient suffering from said pathology an oral sustained-release pharmaceutical composition (*Id.* at p. 31, lines 25-31).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 35, 37-42, 44-55 and 57 are unpatentable under 35 U.S.C. § 103(a) as being obvious over WO 99/44623 to Artman *et al.* (hereinafter "Artman") in view of U.S. Patent No. 4,571,333 to Hsiao *et al.* (hereinafter "Hsiao").

B. Whether claims 40, 44-46, 48-50, and 55 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Hsiao in view of Artman, or Artman in view of Hsiao and further in view of Groshovy *et al.* (hereinafter "Groshovy") Pharmaceutical Journal, No. 2 (1975).

C. Whether the proposed claim amendments raise new issues that would require further consideration or search.

ARGUMENTS

A. Obviousness Rejection Based on WO 99/44623 to Artman *et al.* in view of U.S. Patent No. 4,571,333 to Hsiao *et al.*

Claims 35, 37-39, 41, 42, 47, 51-54, and 57 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/44623 to Artman *et al.* ("Artman") in view of U.S. Patent No. 4,571,333 to Hsiao *et al.* ("Hsiao"). Appellants respectfully traverse this rejection, as hereinafter set forth.

M.P.E.P. 706.02(j) provides that in order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Furthermore, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Appellants submit that the obviousness rejection of claims 35, 37-39, 41, 42, 47, 51-54, and 57 is improper because the cited references do not provide a motivation to combine to produce the claimed invention and do not provide a reasonable expectation of success.

Artman teaches a combination therapy that includes a valerian-related compound and a nonsteroidal antiinflammatory drug ("NSAID"). The valerian-related compound includes a preparation or extract of valerian, such as isovaleramide, isovaleric acid, or a pharmaceutically acceptable salt, ester, or substituted amide thereof. The combination therapy is formulated into a pharmaceutical composition that is a solid or liquid oral dosage form, such as a tablet, a capsule, a gelcap, a powder, a concentrate, an elixir, a tincture, or a syrup.

Hsiao teaches a sustained-release formulation of naproxen. The sustained-release formulation includes 81%-96% by weight of naproxen in a matrix of 4%-9% by weight of hydroxypropylmethylcellulose (HPMC).

The cited references do not provide a motivation to combine to produce the invention of independent claims 35 and 51. To provide a motivation or suggestion to combine, the prior art or

the knowledge of a person of ordinary skill in the art must "suggest the desirability of the combination" or provide "an objective reason to combine the teachings of the references." M.P.E.P. § 2143.01. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *Id.* (emphasis in original). Asserting that a combination of Artman and Hsiao is obvious amounts to an "obvious to try standard" which has consistently been held not to be the standard for obviousness under 35 U.S.C. § 103. *See, e.g., In re Goodwin*, 576 F.2d 375, 377, 198 USPQ 1, 3 (CCPA 1978); *In re Tomlinson*, 363 F.2d 938, 150 USPQ 623 (CCPA 1966). The Federal Circuit has held that:

> "The admonition that 'obvious to try' is not the standard under § 103 has been directed . . . [to cases where] what would have been 'obvious to try' would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."

In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

Appellants respectfully submit that the cited references do not suggest the desirability of the combination or provide an objective reason to combine. As acknowledged by the Examiner, Hsiao does not teach or suggest an oral sustained-release pharmaceutical composition that comprises the recited active compounds of claims 35 and 51 because Hsiao does not teach or suggest any of the active compounds. (Office Action of April 1, 2005, p. 2). Therefore, Hsiao can not teach or suggest that such an active compound is present in the oral sustained-release pharmaceutical composition in an amount of about 40% - 70% by weight.

As acknowledged by the Examiner, Artman does not teach or suggest an oral sustained-release pharmaceutical composition that comprises a gelling agent. *Id.* at p. 3. Therefore, the Examiner relies on the combination of Artman and Hsiao to teach all of the limitations of independent claims 35 and 51. The Examiner states that "it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to prepare the composition of [Artman] . . . in the form of an oral sustained release matrix by adding a sustained release swelling agent, HPMC, because Hsiao teaches that the pain or inflammation treating composition prepared in a matrix with HPMC prolongs the release of the active agent so as to achieve a once-

a-day administration." *Id.* The Examiner also states that "it would have been obvious for a skilled artisan at the time of the instant invention to add valerian extracts, isovaleramide etc. to the anti-inflammatory naproxen containing composition of Hsiao because [Artman] suggests that the combination treats inflammation as well as provides a relief from acute pain and muscular tension" and that it would have been obvious "to add HPMC of Hsiao to the composition of [Artman] . . . because Hsiao teaches that the composition prepared in a matrix with HPMC prolongs the release of the active agent." *Id.* at p. 3 and p. 6.

However, these statements by the Examiner are conclusory and are not based on objective evidence of record because nothing in the cited references, when combined, suggests the desirability of the combination or provides an objective reason to combine. In addition, as described below and in the referenced Rule 132 Declaration, the Examiner's statements reflect a reading of Hsiao that is too broad and that overlook specific teachings in Hsiao that demonstrate that there would have been no motivation to combine the cited references to produce the claimed invention.

Specifically, nothing in Artman suggests the desirability of the combination or provides an objective reason to combine because Artman does not provide any teaching or suggestion that a sustained-release pharmaceutical composition comprising the recited active compound and the gelling agent would be desirable. As described in the Rule 132 Declaration (see ¶4-¶6) and at pages 2 and 5 of the as-filed specification, the Appellants were the first to recognize the short *in vivo* half-life of isovaleramide during the first human clinical trial of isovaleramide. Without the data generated during this human clinical trial, a person of ordinary skill in the art would not have expected that a sustained-release formulation of isovaleramide would be necessary. In other words, before this discovery by the inventors of the above-referenced patent application, there was simply no reason to provide the recited active compounds in a sustained-release composition. The prior knowledge of isovaleramide compositions (*e.g.*, as taught in Artman) and of sustained-release compositions for naproxen (*e.g.*, as taught in Hsiao) do not render obvious the claimed sustained-release pharmaceutical composition and the claimed method of treating a pathology because a person of ordinary skill in the art would have had no reason to formulate any of the recited active compounds into a sustained-release composition.

Hsiao also does not suggest the desirability of the combination or provide a motivation to combine because Hsiao teaches that sustained release formulations are active agent specific, and Hsiao does not teach or suggest that the controlled release formulations taught therein would be relevant to any other active agent, such as one of the recited active compounds in claims 35 or 51. Rather, the teachings of Hsiao are limited to a sustained-release formulation of naproxen. Appellants respectfully submit that only Appellants' present teachings provide such motivation, by recognizing the short half-life of the claimed compounds *in vivo*. Therefore, the Examiner's stated motivation to combine appears to be impermissibly based on hindsight.

Furthermore, Hsiao teaches away from combination with Artman. Hsiao expressly teaches that the development of a sustained-release composition is specific to the active agent. (*See*, Hsiao at column 3, lines 6-23 and the Rule 132 Declaration ¶7-¶8). Hsiao expressly teaches that "different types of controlled release oral dosage forms have been developed, but each has disadvantages which affect its suitability to a particular drug." *Id.* at column 3, lines 6-9 (emphasis added). Hsiao also states that "[w]ide variations in the physico-chemical and pharmacokinetic properties of different drugs impose such varied requirements on the design of controlled drug delivery formulations, that formulations that are suitable for one drug cannot generally be predictably applied to other drugs." *Id.* at column 3, lines 9-14 (emphasis added). Therefore, one of ordinary skill in the art, after reading Artman and Hsiao, would not be motivated to combine these references to produce the claimed invention.

Moreover, even if the cited references were combined, the claimed invention would not be produced. As previously described, the sustained-release formulation of naproxen in Hsiao includes 81-96% by weight of naproxen. Hsiao only teaches sustained-release compositions of naproxen and naproxen sodium and does not teach or suggest a sustained-release composition of another active agent, such as a sustained-release composition of one of the recited active compounds like isovalerimide. Accordingly, the tablets of Hsiao could not also contain about 40% - 70% by weight of the active compound, as recited in the instant claims. Although Artman teaches compositions that include isovaleramide and naproxen, Artman does not teach or suggest that these compositions are a sustained-release formulation, let alone sustained-release compositions that comprise about 40% - 70% by weight of one of the recited active compounds.

In addition, as acknowledged by the Examiner, Hsiao could not be modified to produce the claimed invention because the tablets of Hsiao includes from 81-96% by weight naproxen, which is a substantially higher concentration of the active compound than is recited in claims 35 and 51. (Office Action of April 1, 2005, p. 5-6). Accordingly, even if Artman and Hsiao were combined, the resulting pharmaceutical composition would not include about 40% - 70% by weight of one of the recited active compounds. Furthermore, as evidenced in the Rule 132 Declaration, there is no teaching or suggestion in the cited references that would have lead a person of ordinary skill in the art to produce an oral sustained-release pharmaceutical composition that comprises about 40% - 70% by weight of one of the recited active compounds. (*See*, the Rule 132 Declaration ¶10).

In addition, based on the teachings of Artman and Hsiao, there is no reasonable expectation of success of achieving an oral sustained-release pharmaceutical composition as recited in claim 35 and in the method of claim 51. As previously described, the Examiner's statements reflect a broad reading of Hsiao that overlooks specific teachings that demonstrate that there would have been no expectation of success. Since Hsiao expressly teaches that developing a sustained-release composition is specific to the active agent, a person of ordinary skill in the art, upon reading Hsiao, would not have reasonably expected that adding HPMC according to the teachings of Hsiao to the compositions of Artman would produce a workable oral sustained-release composition that includes each of the characteristics recited in the pending claims. (*See*, the Rule 132 Declaration ¶7-¶10). In fact, the instant specification includes multiple examples in which Appellants experimentally developed a sustained release isovaleramide formulation that would achieve the target steady-state plasma drug concentration. As such, the instant invention was not obvious and required experimentation and inventive step in order to develop the oral sustained-release pharmaceutical composition as recited in the claimed invention.

Furthermore, Appellants emphasize that the claimed range including about 40% - 70% by weight of one of the recited active compounds is nonobvious. The claimed range is not taught or suggested by the art cited against the pending claims, and, as is demonstrated by the experimental findings included in the present application, the claimed range of the recited active compounds facilitates achievement of a pharmaceutical formulation that provides a desired steady state

plasma concentration. In particular, the claimed active compound range of about 40% - 70% by weight allows for sufficient active compound, in combination with a requisite amount of gelling agent and other substances, to create sustained-release formulations that successfully retard the release of the active compound and achieve a targeted steady-state plasma drug concentration.

More particularly, Examples 2 and 3 show that specific formulations provide an oral sustained-release isovaleramide composition that releases a specific amount of the drug over a specific course of time to achieve a specific plasma drug concentration, while minimizing peak to trough differences in plasma drug concentration. (*See*, Specification, p. 33, line 17 to p. 43, line 18). As first recognized by the Appellants, isovaleramide, isovaleric acid and the related compounds cited in the claims have a short half-life *in vivo*. *Id.* at p. 2, lines 1-5. Orally administered isovaleramide in doses from 100 to 1600 mg has a half-life of about 2.5 hours in humans and reaches peak serum concentration in less than an hour after administration. *Id.* at p. 33, lines 1-15. In contrast, a 400 mg isovaleramide dose (44.6% w/w) of the sustained-release formulation I resulted in a peak serum drug concentration in about 4 hours. *Id.* at p. 42, lines 11-16. Sustained-release formulation II, in both 400 mg and 800 mg doses (45.5% w/w) of isovaleramide had peak serum concentrations occurring between 8-12 hours. *Id.* at p. 42, lines 24-26. Sustained-release formulation II, with 1200 mg isovaleramide (45.5% w/w) twice daily, achieves a target therapeutic steady-state plasma drug concentration of 10 μg/ml. Additionally, formulation III, a 1200 mg isovaleramide dose (66.0% w/w), should yield a steady-state plasma concentration averaging about 10 μg/ml for about 12 hours. Accordingly, the specification of the present invention not only teaches the value of sustained-release formulation of the recited compounds, it also specifically supports the value and usefulness of pharmaceutical formulations in a range including about 40% - 70% by weight of one of the recited active compounds. Significantly, the references cited against the pending claims are absolutely devoid of any teaching or suggestion that would lead one of ordinary skill to produce a pharmaceutical formulation including the recited active compounds within the weight range specified in the pending claims. As a result, the cited references could not motivate one of ordinary skill in the art to combine the teachings found within the references in a manner that would produce the claimed invention. Moreover, because they provide no teaching regarding controlled release formulations of the compounds recited in the rejected claims, the references cited against the

pending claims do not provide the ordinarily skilled artisan a reasonable expectation in achieving the subject matter recited in independent claims 35 and 51. Therefore, Appellants respectfully assert that obviousness rejection of claims 35 and 51 is improper and should be withdrawn.

Dependent claims 37-39, 41, 42, 47, 52-54, and 57 are allowable, *inter alia*, as depending from an allowable base claim.

B. Obviousness Rejection Based on Hsiao in view of Artman or Artman in view of Hsiao and further in view of Groshovy.

Claims 40, 44-46, 48-50, and 55 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hsiao in view of Artman or Artman in view of Hsiao and further in view of Groshovy. Appellants respectfully traverse the rejection as to the remaining claims, as hereinafter set forth.

The teachings of Artman and Hsiao are as previously described.

The Examiner relies on Groshovy as teaching a "coating of tablets with intestine soluble film forming polymer such as acetylphthalylcellulose . . . . Groshovy teaches tablets containing valerian extracts are usually destroyed by gastric juices in two hours and the resulting weight loss prompts the addition of plasticizers to the film-forming substances." (Office Action of April 1, 2005, p. 4).

The obviousness rejection of claims 40, 44-46, 48-50, and 55 is improper because the cited references do not provide a motivation to combine to produce the claimed invention and do not provide a reasonable expectation of success. Artman and Hsiao do not provide a motivation to combine or a reasonable expectation of success for substantially the same reasons as discussed above in the obviousness rejection of independent claims 35 and 51. Specifically, since Artman and Hsiao do not provide a motivation to combine to produce an oral sustained-release pharmaceutical composition, Artman and Hsiao necessarily do not provide a motivation to combine to produce a process of preparing such an oral sustained-release pharmaceutical composition. Since Groshovy is limited to the teachings described above, Groshovy does not cure the deficiencies in Artman and Hsiao and, therefore, does not provide a motivation to combine and a reasonable expectation of success.Therefore, the combined teachings of Artman,

Hsiao and Groshovy do not establish the *prima facie* obviousness of independent claim 48, and the obviousness rejection of independent claim 48 should be withdrawn.

Claims 40 and 44-46 depend on claim independent 35, claims 49 and 50 depend on independent claim 48, and claim 55 depends on independent claim 51. Since each of these dependent claims includes all of the limitations of the respective independent claim, each of dependent claims 40, 44-46, 49, 50, and 55 is allowable, *inter alia*, as depending from an allowable base claim.

C. The proposed claim amendments do not raise new issues that would require further consideration or search.

The amendment under 37 C.F.R. § 1.116, filed on September 30, 2005, proposed amendments to claims 35, 37-43, 44-55 and 57 to clarify the claim language and to remove issues with antecedent basis and formalities. However, the proposed claim amendments were not entered.

The MPEP § 714.12, states that any amendment that will place the application either in condition for allowance or in better form for appeal may be entered. Also, amendments filed after a final rejection but before or on the date of filing an appeal, complying with objections or requirements as to form at to be permitted. Appellants submit that the proposed amendments filed on September 30, 2005, do not raise new issues and were made to place the application in condition for allowance and better form for appeal as well as for compliance to requirements as to claim form including antecedent basis and clarity. Therefore, Appellants respectfully request reconsideration and entrance of the proposed claim amendments.

CLAIM APPENDIX

A copy of the currently pending claims is appended hereto as "APPENDIX A."

EVIDENCE APPENDIX

1. A Copy of the Declaration submitted by David S. Wells under 37 C.F.R. § 1.132 is appended hereto as "APPENDIX B."

RELATED PROCEEDINGS APPENDIX

None.

Respectfully submitted,

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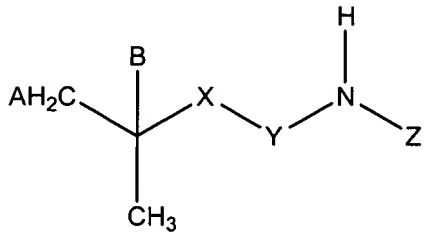
APPENDIX A

LISTING OF THE CLAIMS

Claims 1-34 (Canceled)

35. (Currently amended) An oral sustained-release pharmaceutical composition comprising a core matrix comprising (1) a therapeutically effective amount of an active compound and (2) a gelling agent, wherein the amount of said active compound represents about 40-70% by weight of the composition, and wherein said active compound is selected from the group consisting of: isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, a compound having the structure:



wherein A = H, CH_3, or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH), or -CH_2O-,

Y = -CO-, or –SO_2-, and

Z = H, CH_2CO_2H, or CH_2CONH_2,

and a compound selected from the group consisting of isovaleramide, 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propylsulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate.

Claim 36 (Canceled)

37. (Currently amended) A composition according to claim 35, wherein said composition releases said active compound at a rate sufficient to maintain a therapeutically effective serum concentration of said active compound for at least 8 hours.

38. (Currently amended) A composition according to claim 35, wherein said composition releases said active compound at a rate sufficient to maintain a therapeutically effective serum concentration of said active compound for at least 12 hours.

39. (Currently amended) A composition according to claim 35, wherein said gelling agent comprises xanthan gum.

40. (Currently amended) A composition according to claim 35, wherein said composition has a film-coating that retards access of liquids to the active compound and/or retards release of the active compound through the film-coating.

41. (Currently amended) A composition according to claim 35, further comprising one or more excipients.

42. (Currently amended) A composition according to claim 35, wherein said active compound is isovaleramide.

Claim 43 (Canceled)

44. (Currently amended) A composition according to claim 40, wherein said film coating comprises a polymeric coating material.

45. (Currently amended) A composition according to claim 44, wherein said polymeric coating material comprises a mixture of ethyl cellulose and hydroxypropyl methylcellulose.

46. (Currently amended) A composition according to claim 44, wherein said polymeric coating material further comprises a plasticizer.

47. (Currently amended) A composition according to claim 35, wherein the composition is in the form of a tablet, capsule, or multiparticulate composition.

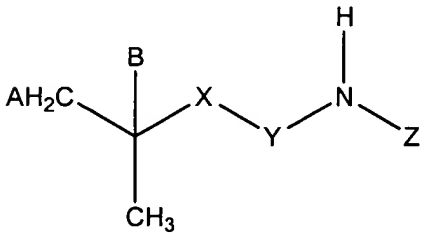
48. (Currently amended) A process for preparing an oral sustained-release pharmaceutical composition comprising a core matrix comprising (1) a therapeutically effective amount of an active compound and (2) a gelling agent, and (3) optionally one or more substances that further retards the release of the active compound, comprising:

(a) mixing together a therapeutically effective amount of an active compound with a gelling agent and optionally one or more substances that further retards the release of the active compound, and

(b) compressing or extruding said active compound, gelling agent, and optional substances that act to sustain release of the active compound,

wherein the amount of said active compound represents about 40-70% by weight of the composition, and

wherein the active compound is selected from the group consisting of: isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, an active compound having the structure:



wherein A = H, CH_3, or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH), or -CH_2O-,

Y = -CO-, or –SO_2-, and

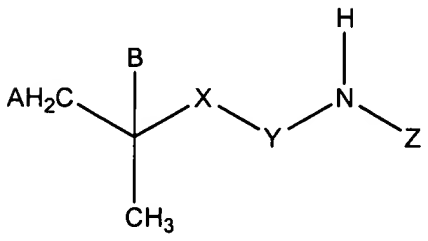
Z = H, CH_2CO_2H, or CH_2CONH_2,

and a compound selected from the group consisting of isovaleramide, 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propylsulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate.

49. (Currently amended) A process according to claim 48, wherein said gelling agent comprises xanthan gum.

50. (Currently amended) A process according to claim 48, further comprising the step of coating the core matrix with a polymer solution to form a film coating.

51. (Currently amended) A method of treating a pathology that is ameliorated by a modulation of CNS activity, wherein said pathology is selected from the group consisting of convulsions, spasticity, affective mood disorder, neuropathic pain syndrome, headache, restlessness syndrome, movement disorder substance abuse/craving, and cerebral trauma, comprising administering to a patient suffering from said pathology an oral sustained-release pharmaceutical composition comprising a core matrix comprising (1) a therapeutically effective amount of an active compound and (2) a gelling agent, wherein the amount of said active compound represents about 40-70% by weight of the composition, and wherein said active compound is selected from the group consisting of: isovaleric acid, a pharmaceutically acceptable salt of isovaleric acid, a pharmaceutically acceptable ester of isovaleric acid, isovaleramide, a active compound having the structure:



wherein A = H, CH_3, or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH), or -CH_2O-,

Y = -CO-, or –SO_2-, and

Z = H, CH_2CO_2H, or CH_2CONH_2,

and a compound selected from the group consisting of 2-methylisovaleramide, 3-methylisovaleramide, 2,2-dimethylisovaleramide, 2,3-dimethylisovaleramide, 4-methylisovaleramide, 2,4-dimethylisovaleramide, 3,4-dimethylisovaleramide, 2,2,4-trimethylisovaleramide, 3-hydroxyisovaleramide, 4-hydroxyisovaleramide, 4-hydroxy-3-methyl-isovaleramide, 2-hydroxyisovaleramide, N-(2-acetamido)isovaleramide, 2-methyl-1-propyl sulfonamide, 1-methylethyl sulfamate, 2-methyl-1-propyl sulfamate, isopropyl carbamate, and isobutylcarbamate,

with the proviso that the treated pathology is not convulsions when the compound is 3-methylisovaleramide, isopropyl carbamate, or isobutyl carbamate.

52. (Currently amended) A method according to claim 51, wherein said sustained-release pharmaceutical composition is in tablet form and the tablet contains a therapeutically effective unit dose of the active compound.

53. (Currently amended) A method according to claim 51, wherein said sustained-release pharmaceutical composition is a multiparticulate composition and the multiparticulate composition contains a therapeutically effective unit dose of the active compound.

54. (Currently amended) A composition according to claim 51, wherein said gelling agent comprises xanthan gum.

55. (Currently amended) A method according to claim 51, wherein said composition further comprises a film-coating comprising a polymeric coating material.

Claim 56 (Canceled)

57. (Currently amended) A method according to claim 51, wherein said active compound is isovaleramide.

Claims 58 and 59 (Canceled)

APPENDIX B

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Wells *et al.*

Serial No.: 09/691,237

Filed: October 19, 2000

For: SUSTAINED-RELEASE FORMULATIONS FOR TREATING CNS-MEDIATED DISORDERS

Confirmation No.: 5026

Examiner: L. Channavajjala

Group Art Unit: 1615

Attorney Docket No.: 1959-7464.1US (N-406-US)

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number: EL995993670US

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Person making Deposit: Steve Wong

DECLARATION

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, David S. Wells, say that:

(1) I, David S. Wells, a coinventor of the above-referenced patent application, am a citizen of the United States currently residing at 127 F Street, Salt Lake City, UT 84103. I received a Ph.D. in Toxicology from the State University of North Carolina in 1985. I have been employed at NPS Pharmaceuticals, Inc. ("NPS") since 1996 and am currently Senior Director of Pharmacokinetics, Drug Metabolism, and Safety Assessment. NPS is the

assignee of record of the above-referenced patent application. I have worked in the pharmaceutical industry since 1985. Before my employment at NPS, I was employed at Wyeth Laboratories (Radnor, PA) and Rhône-Poulenc Rorer (Collegeville, PA), now Sanofi-Aventis. I have spent my 20-year pharmaceutical career working in the field of pharmacokinetics and drug metabolism. During this time, I have worked with a variety of pharmaceutical chemists on the development of prototype formulations for the successful delivery of new chemical entities. These included the controlled-release of an adenosine agonist, the controlled release of a GLP-2 analog, the controlled-release of isovaleramide, the transdermal-permeation of calcitonin, the transdermal permeation of parathyroid hormone, and the intranasal delivery of triamcinolone.

(2) In connection with the captioned application, I have reviewed, and believe that I understand, those portions of the Office Action mailed April 1, 2005, that relate to U.S. Patent No. 4,571,333 to Hsiao *et al.* ("Hsiao") and WO 99/44623 to Artman *et al.* ("Artman"), which are cited in the above-referenced Office Action.

(3) I have read the claims of the above-referenced patent application, as exemplified by independent claims 35, 48, and 51 as amended in response to the Office Action mailed April 1, 2005.

(4) The invention claimed in the above-referenced patent application is based on my and the coinventors' recognition that isovaleramide has a short half-life *in vivo*. The short *in vivo* half-life was discovered by me and the coinventors in 1998, during NPS' first human clinical trial of isovaleramide. From the results obtained in this clinical trial, I calculated the mean plasma clearance of isovaleramide to be approximately 3 ml/minute/kg body weight and the mean plasma half-life of isovaleramide to be approximately 2.5 hours.

(5) It is presently believed that doses of 1200 to 3600 mg/day will provide therapeutically effective plasma concentrations of isovaleramide. However, with a half-life of 2.5 hours,

dosing between 1200 to 3600 mg of isovaleramide per day using an immediate release formulation would result in large differences in peak to trough plasma concentrations. For example, a 2400 mg daily dose (administered as 1200 mg every 12 hours) delivered using an immediate release formulation would result in a mean peak plasma concentration of 27.6 μg/ml, which would decline to a trough concentration of 1.18 μg/ml just prior to the next dose 12 hours later. This 23-fold change in concentration over the dosing period would potentially subject patients to peak concentrations that are undesirably high and trough concentrations that may be subtherapeutic, an unacceptable condition in the treatment of a life-threatening disease, such as epilepsy. In light of the short half-life and predicted dosing range, the coinventors and I recognized the desirability of a sustained release formulation of isovaleramide, which would provide a smaller peak to trough plasma concentration range.

(6) The short half-life of isovaleramide was not predicted and would not have been appreciated without the human clinical trial conducted by NPS in 1988. In this case, hepatocyte metabolism experiments, which are considered to be traditional *in vitro* prediction tools, resulted in a very low level of isovaleramide biotransformation and, thus, did not allow accurate prediction of the *in vivo* half-life results. Therefore, without having the data from the first human clinical trial, the half-life of isovaleramide in humans would have been predicted to be much longer than the half-life actually determined during the human clinical trial. Based on this erroneous prediction of the *in-vivo* half-life of isovaleramide, such large differences in peak to trough plasma concentrations were not expected and the desirability of a sustained release formulation of isovaleramide would not have been appreciated.

(7) Hsiao states that "different types of controlled release oral dosage forms have been developed, but each has disadvantages which affect its suitability to a particular drug." Hsiao at column 3, lines 6-9. Hsiao also states that "[w]ide variations in the physico-chemical and pharmacokinetic properties of different drugs impose such varied

requirements on the design of controlled drug delivery formulations, that formulations that are suitable for one drug cannot generally be predictably applied to other drugs." *Id.* at column 3, lines 9-14. Therefore, as described in Hsiao, the development of a sustained-release composition for a given active compound is a complicated and expensive process. Additionally, providing the active compound in a sustained-release composition can increase the difficulty and costs of the manufacturing process. These statements in Hsiao reflect an understanding, endemic to the field of pharmacokinetics and drug metabolism, that the components of a sustained-release formulation of one active compound will not necessarily provide effective sustained-release of a different active compound.

(8) A person of ordinary skill in the art, working in this field, would not formulate a given active compound into a sustained-release composition without a clinical reason for doing so. This is particularly true in the case of isovaleramide, isovaleric acid, or the related compounds recited in the claims of the above-referenced patent application. Furthermore, a person of ordinary skill in the art would not have expected that adding HPMC as taught in Hsiao's sustained-release naproxen composition to the compositions of Artman would produce a composition that provides sustained-release of an active compound as taught and claimed in the above-referenced patent application.

(9) Prior to our invention and to the disclosure in the above-referenced patent application, a person of ordinary skill in the art would not have undertaken the effort and expense to provide isovaleramide, isovaleric acid, or the related compounds recited in the claims of the above-referenced patent application in a sustained-release composition. In other words, a person of ordinary skill in the art in the field of pharmacokinetics and drug metabolism would not have been motivated, based on the teachings of Artman and Hsiao, to formulate isovaleramide, isovaleric acid, or the other compounds recited in the claims into a sustained-release composition.

(10) The claims in the above-referenced patent application recite "an oral sustained-release composition" wherein the amount of active compound ranges from "about 40% to 70% by weight" of the composition. Hsiao teaches a sustained-release naproxen composition that contains from 81-96% by weight naproxen, a formulation that is unlikely to be successful in delivering isovaleramide at doses up to 3600 mg/day. Hsiao makes no mention of a sustained-release composition that contains a smaller amount of any active compound. Artman is the only cited reference that relates to isovaleramide compositions. However, Artman does not teach sustained-release compositions, let alone sustained-release compositions that comprise from about 40% to 70% by weight of the active compound. Thus, a person of ordinary skill in the art would not find any guidance in Artman and Hsiao that would lead to the production of the claimed oral sustained-release pharmaceutical compositions, which comprise from about 40%-70% by weight of the active compound.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

David S. Wells

29 SEP 2005

Date

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